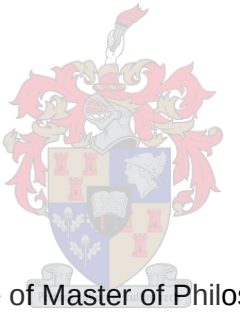
Uterine Carcinosarcoma: A 10-Year Single Institution Experience

by Leana Terblanche (Nee Oberholzer)



Dissertation presented for the Degree of Master of Philosophy in the Faculty of Medicine and Health Sciences, at Stellenbosch University

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Declaration

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Abstract

Objective: This study aimed to determine 5-year progression-free and overall survival in patients with uterine carcinosarcoma, to determine clinical and surgical-pathologic features, to recognize patterns of recurrence and to identify prognostic factors influencing progression-free survival (PFS) and overall survival (OS).

Materials and Methods: A total of 61 patients with uterine carcinosarcoma who were diagnosed between January 2005 and December 2014 were included. Demographic, clinicopathological, treatment and outcome information were obtained. Kaplan-Meier survival analysis and Cox proportional hazards models were used to determine the effects of variables on PFS and OS.

Results: Eighteen patients (29%) presented as FIGO stage I disease, 5 patients (8%) as stage II, 16 patients (26%) as stage III and 22 patients (36%) as stage IV disease, of which 50 patients (82%) had surgery. Seventeen patients presented with recurrence of which 5 (29.4%) were local and 12 (70.6%) were outside the pelvis. Five-year PFS and 5-year OS were 17.3% (CI 8.9%-27.9%) and 19.7% (CI 10.6%-30.8%), respectively. In the univariate analysis, tumour diameter ≥ 100mm (HR 4.57, p-value 0.005) was associated with 5-year PFS and in univariate analysis of OS, a positive family history (HR 0.42, p-value 0.047), receiving a full staging operation (HR 0.37, p-value 0.008) and receiving any other modality of treatment, with or without surgery, (HR 0.48, p-value 0.012) was associated with better survival. An abnormal pap smear (HR 2.4, p-value 0.041), late-stage disease (HR 3.48, p-value < 0.001), presence of residual tumour (HR 3.66, p-value < 0.001), myometrial invasion more than 50% (HR 2.29, p-value 0.019), cervical involvement (HR 3.38, p-value 0.001) and adnexal involvement (HR 3.21, p-value 0.002) were associated with a higher risk of death. In the multivariate analysis, full staging operation was associated with a risk of progression of disease (HR 3.49, p-value 0.025). Advanced stage (HR 4.2, p-value < 0.001) was associated with a higher risk of death. Any other modality of treatment (HR 0.28, p-value < 0.001) and full staging laparotomy (HR 0.27, p-value 0.001) was a protective factor for death.

Conclusions: Carcinosarcoma is an aggressive cancer with poorer survival than previously described. Biological or genetic factors may play a role in our study population. Most recurrences occur outside of the pelvis. Full staging surgery (including pelvic lymphadenectomy) and additional use of other modalities (either for radical or palliative intent) improve survival.

Acknowledgements

I would like to thank my supervisor, Professor MH Botha for his knowledge, support, and guidance.

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Lastly, also my husband, Luther Terblanche. Without his support, this thesis would not have been possible.

Dedications

I would like to dedicate this work to my husband, Luther Terblanche, and my two very young sons, Luther Ulrich Terblanche and Jan-Andries Truter Terblanche.

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List of Abbreviations

BMI: Body mass index

BSO: Bilateral salpingo-oophorectomy

Ca-125: Carcinoma antigen 125

CS: Carcinosarcoma

CT: Chemotherapy

DFS: Disease-free survival

EBRT: External beam radiation therapy

FIGO: International Federation of Gynecology and Obstetrics

GOG: Gynecologic Oncology Group

LVSI: Lymphovascular space invasion

OS: Overall survival

PFS: Progression-free survival

PLND: Pelvic lymph node dissection

RT: Radiotherapy

SEER: Surveillance, Epidemiology, and End Results

TAH: Total abdominal hysterectomy

UCS: Uterine carcinosarcoma

WPI: Whole pelvic irradiation

Glossary

Progression-free survival (PFS): Date of diagnosis to the date of first recurrence or progression of disease, or in absence of recurrence, to the date of the last follow-up or death.

Overall survival (OS): Date of diagnosis to the date of all-cause death or last follow-up.

1 Introduction

Uterine carcinosarcomas are rare, aggressive tumours. No clinicopathological, prognostic or outcome data about this tumour type is known on the African continent. The predictors of progression-free survival and overall survival have not been determined clearly yet. Identifying prognostic factors is important to better define patients who would benefit from relevant treatment strategies and to plan further clinical trials. In this thesis, an extensive literature review will be conducted. A retrospective review of patients treated with uterine carcinosarcoma between 2005 – 2014 at the study institution will be done and the following primary and secondary outcomes will be evaluated:

1.1 Primary outcomes:

- Determination of 5-year overall survival (OS)
- Determination of 5-year progression-free survival (PFS)

1.2 Secondary outcomes:

- Define the clinical characteristics of the patient population
- Describe the surgical-pathological characteristics of the study cohort
- Describe other employed modalities (apart from surgery) in the treatment of patients
- Recognize common sites and patterns of recurrence
- Identify prognostic factors that affect disease-free survival and overall survival in the study population

2 Literature review

2.1 Introduction

Uterine carcinosarcomas are rare, aggressive tumours. Traditionally, they have been considered as a subtype of uterine sarcoma and oncological treatments have been directed against the sarcomatous histological type. They are now regarded as uterine carcinomas. They present with advanced disease in the majority of cases and multiple studies have confirmed their poorer overall survival when compared to high grade endometrioid endometrial carcinomas and other uterine carcinomas high-risk variants[1–6].

2.2 Epidemiology

Their 5-year overall outcome is poor, with survival ranging from 33 to 39%[7,8]. Even in apparent early-stage (disease limited to the uterus), the rate of relapse is more than 50%[9,10]. The worldwide annual incidence according to an old population-based study is between 0.5 and 3.3 cases per 100,000 women and it compromises only 2-3% of uterine cancers[11]. In US-based studies, uterine carcinosarcoma occurs more frequent after age 69 and black race is a significant risk factor for the development of uterine sarcoma and poor survival[11–14]. In a large SEER (Surveillance, Epidemiology, and End Results) analysis, it was confirmed that the total age-adjusted incidence for blacks was two times that of whites and more than twofold that of women of other races[15].

2.3 Classification

Carcinosarcoma (synonyms: metaplastic carcinoma, malignant mixed müllerian - or mesodermal tumour) is classified as a tumour composed of a combination of malignant epithelial and mesenchymal components in the World Health Organization classification of gynaecological neoplasms[16]. Although these tumours are still classified as “mixed” by convention, there is substantial evidence that they are monoclonal in origin and should be considered a subset of endometrial carcinoma. For this reason, they are currently classified in the 2009 FIGO (International Federation of Gynecology and Obstetrics) staging system together with endometrial carcinoma[17].

2.4 Pathology

The carcinomatous component usually consists of a serous (most common) or endometrioid component. Rarely, it may consist of a mucinous, clear cell or squamous cell carcinoma. The sarcomatous homologous component can resemble malignant fibrous histiocytoma, fibrosarcoma, leiomyosarcoma, high grade endometrial stromal sarcoma, undifferentiated sarcoma or a mixture thereof. If there is a heterologous element present, it most frequently contains cartilage or malignant skeletal muscle resembling either embryonal rhabdomyosarcoma or pleomorphic rhabdomyosarcoma. Osteosarcoma or liposarcoma can

also be present. Neuronal, glial, yolk sac, melanocytic, trophoblastic and angiomatoid differentiation may be encountered[18].

Molecular, histopathological and clinical data have confirmed that most uterine carcinosarcomas are derived from a single stem cell and are in fact monoclonal in origin. The sarcomatous element is derived as a result of dedifferentiation of the carcinomatous component, and the carcinomatous component is the dominant part of this tumour. Clinical data in support of the above hypotheses is the fact that uterine carcinosarcoma shares similar risk factors to endometrial carcinoma. Both are associated with nulliparity, exogenous estrogen use, obesity and oral contraceptives are known to offer a protective effect against their development. Also, both may occur in association with previous radiation exposure or tamoxifen therapy[19–24]. The location and pattern of sites of metastatic disease in uterine carcinosarcoma resemble that of aggressive endometrial cancer rather than uterine sarcomas (lymphatic rather than hematogenous)[25,26]. Similarly, most deaths in patients with uterine carcinosarcoma are due to recurrent abdominal or local pelvic disease rather than distant metastatic disease[9]. Histopathological studies have shown that metastatic tumour deposits and tumour emboli in lymphovascular channels almost always consist of the carcinomatous elements[25,27]. Pure/Coexistent sarcomatous elements are uncommon in metastatic foci. Immunohistochemical studies have shown the expression of epithelial markers in the sarcomatous element[28] and other studies have confirmed concordance of p53, p16 and PAX8 staining between the sarcomatous and carcinomatous components in single tumours[29–31]. The dominant role of the carcinomatous component in carcinosarcoma is emphasized by immunohistochemical studies showing more expression of proteins involved in angiogenesis, higher mitotic and proliferation index, lower apoptotic index in the carcinomatous component compared to the sarcomatous component[32–34]. Lastly, clonality studies confirmed the monoclonal origin of the epithelial and stromal components in carcinosarcomas[35]. The presence of tumours with a distinct biclonal origin has been reported but the clinical implications and prognosis of this cohort are not yet well-defined[36].

2.5 Prognostic factors

Several pathological factors have been associated with recurrence and survival. These include age, disease stage, positive cytology, myometrial invasion depth, LVSI (Lymphovascular Space Invasion), adnexal and serosal involvement, abnormal Ca-125 levels, residual tumour greater than 1cm, performance status 2 to 4, lymph node metastases and number of lymph nodes collected [37–41]. The prognostic significance of the existence of heterologous versus homologous sarcomatous components is controversial. Several studies have found that the presence of heterologous elements carries no prognostic significance[39,42,43], but others have found it to be a powerful negative prognostic factor[3,9,44].

2.6 Management of uterine carcinosarcoma

2.6.1 Surgical management

Due to the rarity of uterine carcinosarcoma, prospective trials to establish optimal treatment regimens are limited and most evidence-based treatment algorithms are based on mostly retrospective studies. The National Comprehensive Cancer Network (NCCN) recommends a total abdominal hysterectomy, bilateral salpingo-oophorectomy and pelvic nodal dissection. It also states that para-aortic nodal evaluation may be utilized for staging and omental biopsy should also be performed. Maximal tumour debulking of gross disease should also be considered[45].

Studies supporting aggressive surgical cytoreduction in advanced-stage uterine carcinosarcoma are lacking. The principle and benefit of cytoreductive surgery are largely unknown in this population. Only two retrospective studies to date evaluated the role of cytoreductive surgery in this population group. One retrospective study evaluated the role of complete gross resection in stage III-IV uterine carcinosarcoma and did demonstrate that resection to no visible disease was associated with improved overall survival (52.3 versus 8.6 months)[46]. A multi-institutional retrospective study from the Japanese gynecologic oncology group also concluded that optimal cytoreductive surgery (to residual tumour less than 1cm) and pelvic lymph node dissection are associated with improved OS in advanced uterine carcinosarcoma patients (median OS 37.9 versus 18 months)[47]. A literature review that was published by Vorgias et al.[7] discussing and evaluating the role of lymphadenectomy in uterine carcinosarcomas, concluded that it is mandatory for staging purposes and that most retrospective studies confirm a significant survival advantage. The potential mechanisms for the improvement in survival are postulated to be from the removal of micro-metastatic foci, reduction of recurrence risk (removal of ‘‘target tissue’’) and mechanical circumvallate. Likewise, studies are also in support of performing omentectomy[48,49].

2.6.2 Adjuvant therapy

The role of adjuvant treatment in carcinosarcoma is controversial and still debated in the literature. Approximately 50% of patients with surgical stage I carcinosarcoma who do not receive adjuvant therapy will experience a recurrence and most of them will recur distally[50]. There is no clear agreement about the best possible adjuvant treatment (chemotherapy, radiation or a combination thereof) and no alternative treatment approaches exist for various disease stages. Randomized trials are limited due to the rarity of this tumour type and most institutions have their own individualized adjuvant treatment approach.

2.6.2.1 Chemotherapy

Recommendations for adjuvant chemotherapy in early-stage disease are not based on strong evidence. Only limited retrospective data are available to guide treatment. One of the largest

multi-institutional reviews to date found that adjuvant chemotherapy was significantly associated with improved PFS and OS was improved only in the absence of LVSI[51]. In patients with advanced-stage disease, adjuvant chemotherapy can be considered, but the optimal chemotherapeutic regime is still being investigated.

A Gynecologic Oncology Group randomized phase III trial (GOG 150) of whole abdominal irradiation (WAI) versus cisplatin-ifosfamide and mesna (CIM) as post-surgical therapy in stage I-IV uterine carcinosarcoma did not find a statistically significant advantage in recurrence rate or survival for adjuvant CIM over WAI. However, the observed differences favoured the use of combination chemotherapy[52]. Another GOG randomized phase III trial in advanced uterine carcinosarcoma demonstrated a superior OS for combination chemotherapy (ifosfamide with paclitaxel) compared with single-agent treatment (ifosfamide alone)[53]. GOG 261, the latest randomized phase III trial comparing the combination of carboplatin and paclitaxel versus the combination of ifosfamide and paclitaxel for UCS, is ongoing (NCT00954174).

2.6.2.2 Neoadjuvant chemotherapy

The role of neoadjuvant chemotherapy in UCS is not well described. Only one nested case-control study within a multicenter retrospective cohort examined the role of neoadjuvant chemotherapy in patients with stage IV UCS[54]. Patients who received neoadjuvant chemotherapy followed by hysterectomy-based surgery for stage IV UCS were compared to women who had primary hysterectomy-based surgery without neoadjuvant chemotherapy. The analysis showed no statistically significant difference in survival outcomes between these two groups of women with advanced uterine carcinosarcoma.

2.6.2.3 Radiotherapy

The role and benefit of radiotherapy in die adjuvant setting in patients treated surgically for UCS are controversial. Numerous small retrospective series have studied the benefit of adjuvant radiotherapy in UCS. Most have shown a consistent decrease in pelvic failures, but no significant effect on overall survival[55–60]. Some studies have claimed an OS benefit with adjuvant pelvic irradiation for patients with stage I-II disease[61,62] and some only for stage I disease[63]. Others have shown no benefit in terms of local control or overall survival rates[64]. In a large National Cancer Database review[65], EBRT (External Beam Radiation Therapy) and brachytherapy combination were associated with an overall survival advantage in the adjunctive setting of uterine carcinosarcoma, but not among those receiving EBRT or brachytherapy alone. A large SEER analysis including 1 891 women with early-stage UCS demonstrated that overall survival with pelvic radiotherapy was only improved in patients who did not receive lymphadenectomy as part of the initial surgery and only had a small effect on survival in women with negative nodes[66]. This is in contrast to another large SEER analysis which demonstrated that adjuvant radiation therapy had no improvement in overall survival regardless of lymphadenectomy in patients with stage I-III disease[67]. A randomized phase III

trial conducted by the European Organization for Research and Treatment of Cancer, evaluated the role of adjuvant pelvic radiotherapy for early-stage uterine sarcomas (including 91 patients with UCS)[68]. Their results were consistent with most of the retrospective studies – confirming a trend towards better local control (but also higher distant metastatic rate) and no significant impact on either PFS or OS. In the Gynecologic Oncology Group 150 trial[52] (mentioned previously) comparing whole abdominal irradiation and cisplatin-ifosfamide with mesna as adjuvant therapy, patients in the irradiation group were likely to experience abdominal recurrence and serious late adverse events. Patients receiving chemotherapy only had a higher probability to experience a vaginal recurrence.

2.6.2.4 Combination therapy

The findings of GOG 150[52] estimated high crude probabilities of recurrence in both radiation and chemotherapy arms (52% relapse rate at 5 years in the chemotherapy arm and 58% in the radiation arm). Also, the patterns of failure/recurrence between the WAI and CIM group (increased vaginal recurrence rate in the chemotherapy cohort versus the radiotherapy cohort; notable reduction in abdominal failures in the chemotherapy group as compared to the WAI arm) led to the consideration of a combination of radiation and chemotherapy following surgery. The optimal schedule and sequence remain controversial, but several recent retrospective and prospective non-randomized trials suggest a longer survival. They are briefly discussed:

- A phase 2 prospective trial of ‘sandwich’ multimodality therapy in UCS reported it as an efficacious regimen for surgically staged UCS patients, but that the efficacy of this ‘sandwich’ regimen comes with a moderate, but tolerable toxicity profile[69].
- A retrospective, multi-institutional review that aimed to characterize the impact of adjuvant therapy on survival in women with stage I-II UCS after primary surgery, demonstrated a significantly lower risk of death in women treated with combined chemotherapy and radiation compared with women undergoing observation, adjuvant radiation only or adjuvant chemotherapy alone. Freedom from vaginal recurrence was also improved with adjuvant chemoradiation[70].
- In a pilot study of 38 patients with clinical stage I or II UCS who underwent surgical staging and adjuvant radiation and chemotherapy, survival rates of 74% were obtained[71].
- A retrospective review of the Memorial Sloan-Kettering Cancer Centre medical records of completely resected stage I-IV UCS with rhabdomyosarcoma differentiation suggested that chemotherapy alone or in combination with radiotherapy is associated with longer PFS and OS compared to RT alone[72].
- In a retrospective study between different postoperative treatment modalities for uterine carcinosarcoma conducted by Menczera et al., chemotherapy, whole pelvic

irradiation (WPI) and sequential treatment (i.e., chemotherapy followed by WPI) were compared. It was found that the highest median survival and 5-year survival rate was observed in the sequential treatment group[73].

- In a recent retrospective review by Gungorduk et al.[74], sequential treatment after surgery decreased mortality significantly in both early and advanced-stage disease. In early-stage patients (I-II) who received adjuvant chemotherapy with radiation therapy, the median DFS and OS were 44 months and 55 months, respectively, compared to 34.5 months and 36 months, respectively, in patients who received adjuvant radiotherapy or chemotherapy alone. In advanced-stage patients (III-IV), the median DFS and OS of patients receiving adjuvant radiotherapy with chemotherapy were 25 months and 38 months, respectively, compared to 23.5 months and 24.5 months, respectively, in patients receiving adjuvant radiotherapy or chemotherapy alone.
- Odei et al.[75] conducted one of the largest retrospective analyses evaluating the patterns-of-care and overall survival benefit of adjuvant chemoradiation compared with adjuvant chemotherapy among UCS patients. The findings concluded that, when compared with adjuvant chemotherapy alone, the use of adjuvant chemoradiation in UCS patients was associated with a significant OS benefit. However, multiple demographic and clinical factors significantly influenced the choice of adjuvant therapy.
- A multi-institutional study of outcomes in stage I-III uterine carcinosarcoma (n=303), evaluated the use of adjuvant therapy after primary surgery for stage I-III UCS. Observation was associated with a fourfold increased risk of death compared to chemotherapy. Multimodality therapy for women with stage I-II disease was associated with improved PFS compared to chemotherapy alone[76].
- In the USA, the National Cancer Database hospital registry was used to analyse patterns of adjuvant chemotherapy and radiotherapy and to assess the impact on survival of each of these treatment regimens in 4 906 patients with UCS confined to the pelvis who underwent primary surgery[77]. The 5-year OS for patients receiving no adjuvant therapy, adjuvant RT alone, adjuvant CT alone, and combined CT and RT were 44.9%, 47.1%, 47.5%, and 62.9%, respectively. The study group concluded that combination therapy with chemotherapy and radiotherapy was associated with significantly improved 5-year OS compared with no further therapy, radiotherapy alone, or chemotherapy alone.
- In a matched cohort analysis in stage 1 UCS (5 614 women identified from the National Cancer Database) to determine if lymphadenectomy, chemotherapy and radiotherapy were associated with survival, it was concluded that removal of at least

15–20 nodes were associated with increased survival. Also, vaginal brachytherapy with multiagent chemotherapy was associated with increased survival[78].

- In another large National Cancer Database analysis (which included 10 609 patients with stage I-IV disease), the objective was to evaluate rates of chemotherapy and radiotherapy delivery in the treatment of UCS and to compare clinical outcomes of treated and untreated patients. The lowest hazard ratio for deaths observed was in patients that received chemoradiation[79].
- In a study aimed to evaluate the impact of radiation therapy in 155 women with stage I-III UCS[80], EBRT was associated with higher 5-year pelvic disease control and overall survival. Also, treatment with concurrent chemoradiation therapy was independently associated with a higher disease-specific survival rate on multivariate analysis (compared with any other or no treatment).

2.6.2.5 Targeted therapy

Despite advances in the treatment of UCS, the prognosis remains poor. Recently, immunotherapy targeting known dysfunction molecular pathways have been developed. In a recent systematic review[81], the differential expression and accessibility of epithelial cell adhesion molecule-1 on metastatic/chemotherapy-resistant UCS cells in comparison to normal tissues and Human Epidermal Growth Factor Receptor 2 (HER2) was identified as new potential possibilities in the field of target therapy. The impact of these new therapies on survival rates are currently unknown but is being studied.

The role of hormonal therapy is unclear and has not been studied in UCS. One case report described by Wang et al.[82], reported a case of a 69-year old woman with recurrent metastatic UCS that responded well to letrozole therapy. The tumour shrunk to less than 25% of its original volume.

2.7 Conclusion

Most strategies currently used in the treatment of uterine carcinosarcoma are derived from retrospective data. Few prospective trials are available to inform optimal treatment. From the available data, it seems that women with early-stage UCS will benefit from chemotherapy for systemic control and radiotherapy for local control. Women with advanced disease should benefit from aggressive cytoreduction followed by combination chemotherapy and radiation for local control. In unresectable disease, neoadjuvant chemotherapy followed by surgery is a feasible option. Quality of life studies is needed to justify the increased toxicity with multimodal adjuvant therapy.

3 Material and Methods

Ethical approval was obtained from the Stellenbosch University Health and Research Ethics Committee (HREC). A waiver of consent was also obtained.

The database of the Unit for Gynecological Oncology at Tygerberg Hospital was reviewed to identify patients with pathologically confirmed uterine carcinosarcoma treated between January 1st, 2005 and December 31st, 2014. 61 Patients were identified. Demographic, medical, surgical, pathological, follow-up and survival data were collected from all patients. Patients were staged according to the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system for endometrial carcinoma. Staging groups were classified as early FIGO stage (I-II) and advanced FIGO stage (III-IV). In our unit, we regard a full staging laparotomy for uterine carcinosarcoma as a total abdominal hysterectomy (TAH) with bilateral salpingo-oophorectomy (BSO), infracolic omentectomy and bilateral pelvic lymphadenectomy with washings and peritoneal biopsies. Complete debulking was defined as a procedure where no residual macroscopic tumour was left behind during surgery.

Adjuvant therapy or palliation management was individualized after discussion at a multidisciplinary tumour board meeting and was based on the age of the patient, stage of disease, performance status and medical co-morbidities. Patients returned for follow-up evaluation (review of symptoms and full clinical examination) after completing treatment every three months for the first two years, every six months for the next three years, and annually thereafter. Imaging was only performed if recurrence was suspected. Survival data was censored in August 2018.

4 Statistical analysis

Progression-free survival (PFS) was defined as the date of diagnosis to the date of first recurrence or progression of disease, or in absence of recurrence, to the date of the last follow-up or death. Overall survival (OS) was calculated from the date of diagnosis to the date of death or last follow-up. For the time to progression, the competing risk of death had to be considered since this state prevented a participant to experience the progression event. A competing risks survival analysis of progression was done with death as the competing risk. Univariate and multiple regression models were considered for this outcome. The small sample size and number of events was a limiting factor on the complexity of the multiple regression model. Overall survival was modelled using a Cox proportional hazards model. Univariate and multiple regression models were considered. Hazard ratios and 95% confidence intervals were estimated and reported. Kaplan-Meier plots were done to depict the survival or incidence curves. As descriptive statistics, two-way tables of the events and the risk factors were tabulated.

A 5% significance level was used in this study. The Stata15 software package was used for statistical analysis.

5 Results

5.1 Clinical characteristics of the study cohort

We identified 61 patients with uterine carcinosarcoma during the study period. Clinical characteristics of the patients are shown in Table 5-1. The mean age at diagnosis was 66 years and most patients were postmenopausal (97%). Most patients presented with abnormal uterine bleeding (90%), pain (26%), loss of weight (21%) and abnormal discharge (15%). Other less common presentations included loss of appetite, fatigue, shortness of breath, nausea and vomiting, constipation and dysuria. Hypertension (52 patients) and diabetes (20 patients) were the most common comorbid diseases. Pap smear results were available for 44 patients. Twenty-nine patients had an abnormal pap smear. The detection rate of a pap smear to detect uterine malignancy in our UCS population was 65.91%. Only 2 patients were on tamoxifen for previously treated breast cancer and no patients had a history of previous pelvic radiotherapy (only 1 patient had a history of breast radiation as part of her treatment for breast cancer). Eighteen patients presented as FIGO stage I disease, 5 patients as FIGO stage II, 16 patients as FIGO stage III and 22 patients presented as FIGO stage IV disease.

Five-year overall survival was 19.7% (95%CI 10.6%-30.8%). This is shown in Figure 5-1. Five-year progression-free survival (taking both progression and death as event) was 17.3% (95%CI 8.9%-27.9%). In fact, this progression-free survival is the same as the two-year progression-free survival estimate since no event of progression was observed after two years. This is shown in Figure 5-2. A 2-year progression-free survival estimate is more realistic as only 8 patients in our cohort were still alive after 5 years of follow-up.

Table 5-1: Clinical characteristics of the study population

Characteristic	**Value (n=61)**
Mean age at diagnosis, years (range)	66.77 (35.08-81.6)
Gravidity (median)	4
Parity (median)	4
BMI (kg/m2)	
Mean (range)	32.86 (20.60-56.24)
Menopausal status	**No (%)**
Premenopausal	2 (3.28)
Postmenopausal	59 (96.72)
Presenting complaint*	
Abnormal uterine bleeding	55 (90.16)
Pain	16 (26.23)
Loss of weight	13 (21.31)
Abnormal discharge	9 (14.75)
Other	9 (14.75)
Comorbid diseases*	
Hypertension	52 (85.25)
Diabetes	20 (32.79)
Osteoarthritis	7 (11.48)
Ischemic heart disease	6 (9.83)
Hypercholesterolemia	6 (9.83)
History of breast cancer	4 (6.56)
Other	11 (18.03)
Family history of cancer[#]	
Yes	11 (18.03)
No	49 (80.33)
Unknown	1 (1.64)
Pap smear results	
Result not available	17 (27.87)
Unsuitable for interpretation	2 (3.28)
Normal	13 (21.31)
Abnormal	29 (47.55)
Pre-operative biopsy results	
Suggestive of carcinosarcoma	32 (52.46)
Suggestive of other malignancy or poorly differentiated tumour	22 (36.07)
Not done/unsuitable for diagnosis	7 (11.48)
HIV status	
Negative	55 (90.16)
Positive[$]	1 (1.53)
Unknown	5 (8.20)
RPR status	
Negative	52 (85.25)
Positive	1 (1.64)
Unknown	8 (13.11)
Figo Stage presentation	
Figo I	18 (29.51)
Figo II	5 (8.20)
Figo III	16 (26.23)
Figo IV	22 (36.07)
Five-year progression-free survival	17.3% (CI 8.9%-27.9%)
Overall 5-year survival	19.7% (CI 10.6%-30.8%)

***Some patients presented with a combination of factors
[#]First degree relative only of any cancer
[$]CD4 count 458

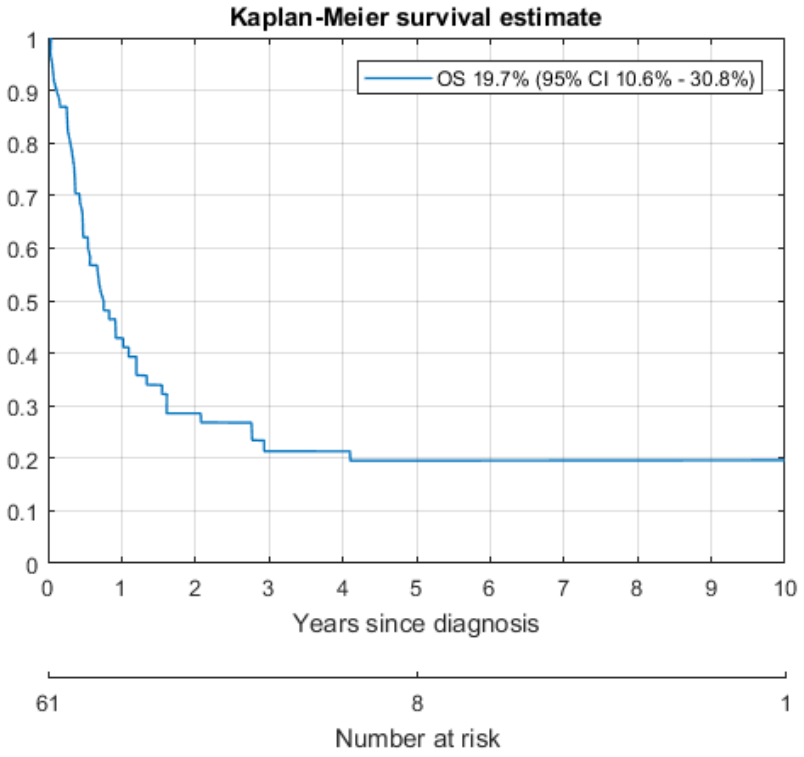

Figure 5-1: Kaplan-Meier curve depicting 5-year overall survival.

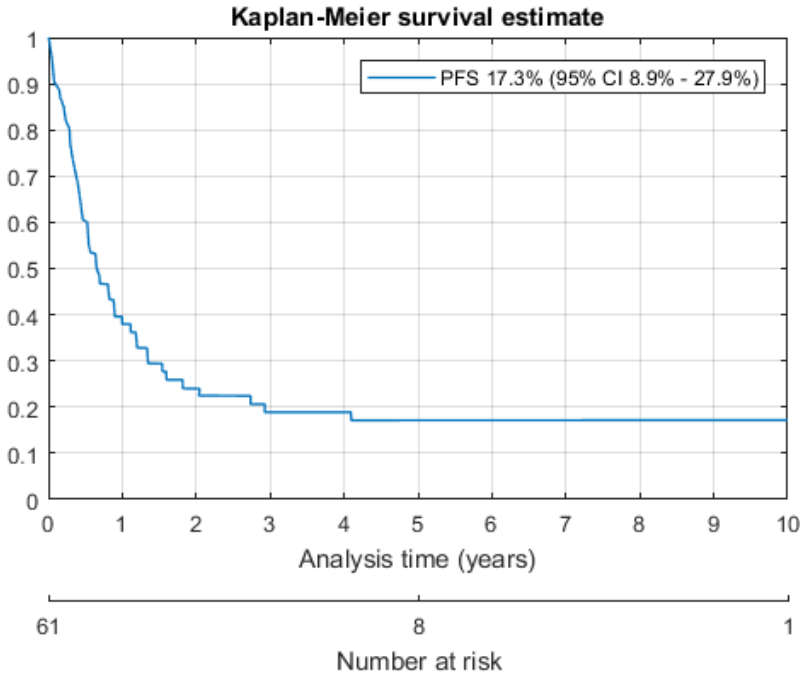

Figure 5-2: Kaplan-Meier curve depicting 5-year progression-free survival.

5.2 Surgical-pathological characteristics of the study cohort

The surgical management and debulking status of patients are summarized in Table 5-2 and histopathological data is given in Table 5-3. Eleven of the 61 patients did not undergo surgery. This was due to advanced disease at presentation (5 patients), not being surgical candidates due to medical conditions (4 patients), and 2 patients declining surgery. Only 11 patients received a TAH/BSO/Omentectomy/PLND. Complete debulking (no macroscopic tumour) was obtained in 28 patients and 14 patients had incomplete debulking (any macroscopic tumour left). In patients that received a pelvic lymphadenectomy, the mean lymph node yield per patient was 19 nodes.

Table 5-2: Surgical management and debulking status of patients

Surgical procedures performed	**No. (%) (n=61)**
TAH/BSO/Omentectomy/PLND[&]	11(18)
TAH/BSO/PLND/evaluation of omentum	4(6.6)
TAH/BSO/Omentectomy[$]	8(13.1)
TAH/BSO*	18(29.5)
TAH	2(3.3)
Subtotal hysterectomy/BSO/Omentectomy	1(1.6)
Subtotal hysterectomy/Omental biopsy	1(1.6)
Surgery aborted(open/close)	5(8.2)
No surgery	11(18)
Debulking status	**(n=50)**
Complete debulking	28(56)
Incomplete debulking	14(28)
Unknown	8(16)
Lymph nodes	**(n=15)**
Total amount of lymph nodes removed	284
Mean (range)	19(1-43)
Number of node-positive patients	4(26.7)
Number of positive nodes	7(2.5)

[&]Includes one patient that had additional sigmoidectomy with a Hartmann's pouch and colostomy as part of debulking
[$]Includes one patient that had a rectosigmoidectomy with a Hartmann's pouch and colostomy
*Includes one patient that had a vaginal hysterectomy and BSO

Table 5-3: Histopathological tumour data

Histopathological tumour data	**No (%) (n=61)**
Tumour diameter (mm)*	
Mean(range)	90.22(10-300)
Histopathological type#	
Homologous	11(18.03)
Heterologous	40(65.57)
Unknown/not reported	10(16.40)
LVSI#	
Yes	15(24.60)
No	23(37.70)
Unknown	23(37.70)
Myometrial invasion	
<1/2	21(34.42)
>1/2	29(47.54)
Unknown	11(18.03)
Lower segment involvement	
Yes	26(42.62)
No	16(26.22)
Unknown	19(31.14)
Cervical involvement#	
Yes	23(37.70)
No	24(39.34)
Unknown	14(22.95)
Adnexal spread	
Yes	14(22.95)
No	33((54.10)
Unknown	14(22.95)
Necrosis#	
Yes	41(67.21)
No	7(11.47)
Unknown	13(20.00)

*Determined on surgically resected specimen (information only available in 41 patients)
#Determined on biopsy or surgically resected specimen

5.3 Other employed modalities in the treatment of patients

Non-surgical, adjuvant and palliative treatment was individualized for each patient after multidisciplinary discussion. Other modalities employed were chemotherapy, radiation therapy or hormonal therapy. Only 33 patients (54%) of the entire cohort received some form of other therapy – either as part of curative intent or for palliation purposes. A summary of the modalities is given in Table 5-4.

Table 5-4: Other modalities employed in the treatment of patients

Modality employed	Number (%) (n=61)
WPI plus brachytherapy	7(11.5)
WPI	3(4.9)
Brachytherapy	5(8.2)
Chemotherapy and vault brachytherapy	2(3.3)
Chemotherapy and WPI	1(1.6)
Chemotherapy	5(8.2)
Palliative radiotherapy*	9(14.8)
Palliative hormonal therapy	1(1.6)
No other modality employed	28(45.9)

*Including high-dose palliation WPI or single fraction radiotherapy

5.4 Recurrence of disease

Seventeen patients presented with documented recurrence (diagnosed clinically or radiologically). Of these 17 recurrences, 5 patients (29.41%) were initially early stage (FIGO stage I or II). The sites of recurrences are tabulated in Table 5-5. Five patients (29.41%) presented with local recurrence only and 12 patients (70.59%) presented with recurrence outside the pelvis with or without local recurrence). Of the 5 patients that presented with local recurrence, none had adjuvant therapy after initial management. Of the 12 patients that presented with recurrence outside the pelvis, only 7 patients (58%) received adjuvant treatment and chemotherapy was included in only 4 of the regimens.

Table 5-5: Sites of recurrences

Site of Recurrence	Number (%) n=17
Pelvis (local)	5(29.41)
Abdominal	1(5.89)
Distant	3(17.65)
Pelvic and abdominal	2(11.76)
Abdominal and distant	5(29.41)
Pelvis, abdominal and distant	1(5.89)

5.5 Identification of prognostic factors associated with progression and overall survival

The results of univariate and multivariate analysis are summarized in Table 5-6 and Table 5-7. In univariate analysis of PFS, only tumours with a diameter equal or more than 100mm (HR 4.57, p-value 0.005) was a significant factor for progression, but data were only available for 41 patients. In univariate analysis of OS, several variables were statistically significant. A positive family history (HR 0.42, p-value 0.047), receiving a full staging operation (HR 0.37, p-value 0.008) and receiving any other modality of treatment (HR 0.48, p-value 0.012) were associated with better survival, while an abnormal pap smear (HR 2.4, p-value 0.041), late-stage disease (HR 3.48, p-value <0.001), presence of residual tumour (HR 3.66, p-value < 0.001), myometrial invasion more than 50% (HR 2.29, p-value 0.019), cervical involvement (HR 3.38, p-value 0.001) and adnexal involvement (HR 3.21, p-value 0.002) were associated with higher risk of death.

Table 5-6: Univariate analysis of PFS and OS in patients with uterine carcinosarcoma (significant p-values in bold)

Variable	Progression-free survival			Overall survival		
	Hazard ratio	95%CI	p-value	Hazard ratio	95% CI	p-value
Age (> 60yr vs <60yr)	1.20	0.35-4.13	0.771	1.1	0.53-2.28	0.794
Family history (yes vs no)	1.00	0.29-3.51	0.999	0.42	0.18-0.99	**0.047**
Pap Smear (abnormal vs normal)	1.45	0.43-4.89	0.548	2.40	1.03-5.60	**0.041**
Stage (late vs early)*	1.54	0.56-4.25	0.400	3.48	1.79-6.77	**0.000**
Residual tumour (yes vs no)	0.41	0.13-1.32	0.135	3.66	1.90-7.02	**0.000**
Histology (homologous vs heterologous)	0.44	0.10-1.88	0.270	0.71	0.31-1.62	0.418
LVSI (positive vs negative)	0.78	0.27-2.22	0.639	1.38	0.77-3.47	0.200
Myometrial invasion > 50% (yes vs no)	0.67	0.26-1.72	0.403	2.29	1.15-4.57	**0.019**
Lower segment involvement (yes vs no)	1.39	0.50-3.89	0.529	1.86	0.89-3.90	0.098
Cervical involvement (yes vs no)	1.61	0.63-4.13	0.325	3.38	1.64-6.97	**0.001**
Adnexal involvement (yes vs no)	0.663	0.21-2.05	0.475	3.21	1.56-6.63	**0.002**
Necrosis (yes vs no)	2.45	0.34-17.60	0.372	1.97	0.70-5.58	0.200
Tumour diameter =>100mm (yes vs no)	4.57	1.59-13.19	**0.005**	1.75	0.75-4.07	0.192
Full staging (yes vs no)	2.42	0.94-6.27	0.069	0.37	0.18-0.78	**0.008**
Any other modality treatment[#] (yes vs no)	0.70	0.27-1.80	0.455	0.48	0.27-0.85	**0.012**

*Early-stage regarded as FIGO stage I and II and late-stage as Figo stage III and IV

[#]Including chemotherapy, radiation or hormonal therapy – as part of curative or for palliation intent

Due to the limited sample size and some missing data, all the variables could not be tested in the multiple regression models. In the multivariate analysis, only full staging surgery was statistically significant associated with a risk of progression of disease (HR 3.49, p-value 0.025). Advanced stage (HR 4.2, p-value < 0.001) was statistically significant associated with a higher risk of death. Any other modality of treatment (HR 0.28, p-value < 0.001) and full staging surgery (HR 0.27, p-value 0.001) was a protective factor for death. Kaplan-Meier survival estimates according to the stage of disease, receiving any other modality of treatment and receiving a full staging procedure is shown in Figure 5-3 to 5-5.

As tumour diameter (≥100mm) was a significant factor associated with progression in the univariate analysis, the same regression model was used by including this variable as well (data not shown). However, as tumour diameter data was only available for 41 patients, multiple regression could only be applied to 41 patients. Tumour diameter ≥ 100mm was a risk factor for progression (HR 10.35, p-value 0.011, CI 1.72-62.1), but the confidence intervals were extremely wide due to the small number of events and adjustments. It was not a significant factor in OS (HR 2.09, p-value 0.110, CI 0.85-5.17). Imputation analysis to account for the missing tumour diameter indicators data, using a logistic regression imputation model with covariates of age and stage, was also attempted. Tumour diameter ≥100mm was no longer a significant factor in progression of disease (HR 4.64, p-value 0.086, CI 0.80-26.94) or overall survival (HR 1.66, p-value 0.221, CI 0.73-3.78). The true association of tumour diameter on progression is therefore uncertain.

Table 5-7: Multivariate analysis of factors influencing PFS and OS (significant p-values in bold)

Variable	**Progression-free survival**			**Overall survival**		
	Hazard ratio	**95%CI**	**p-value**	**Hazard ratio**	**95% CI**	**p-value**
Age	1.34	0.36-4.96	0.657	0.79	0.38-1.65	0.526
Stage (late vs early)	2.39	0.69-8.31	0.172	4.20	2.09-8.44	**0.000**
Any other modality treatment (yes vs no)	0.67	0.27-1.70	0.401	0.28	0.15-0.53	**0.000**
Full staging (yes vs no)	3.49	1.17-10.41	**0.025**	0.27	0.12-0.59	**0.001**

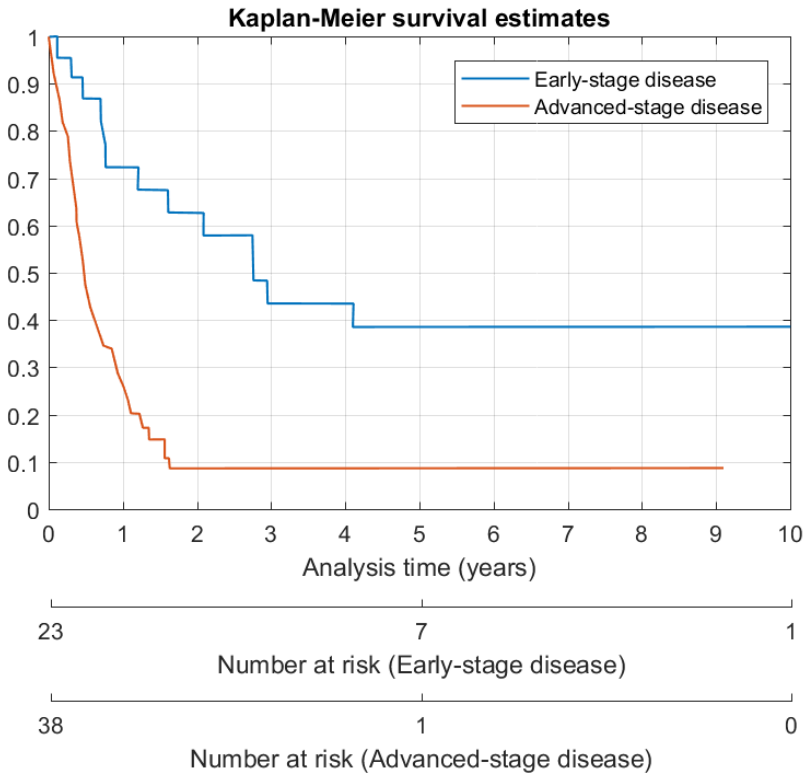

Figure 5-3: Overall survival according to the stage of disease.

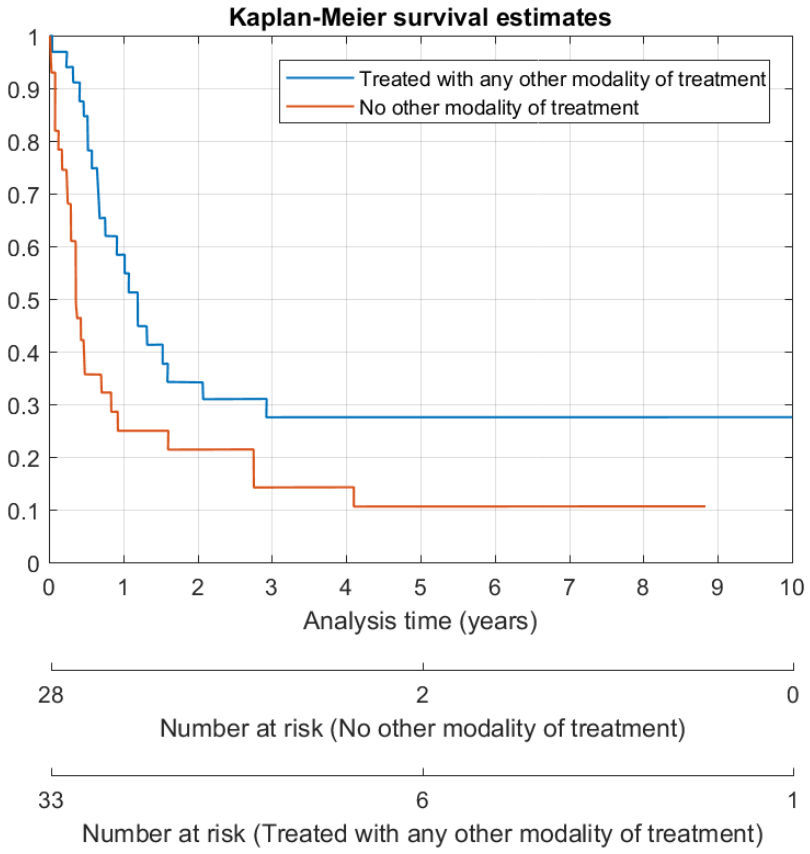

Figure 5-4: Overall survival according to receiving any other modality of treatment

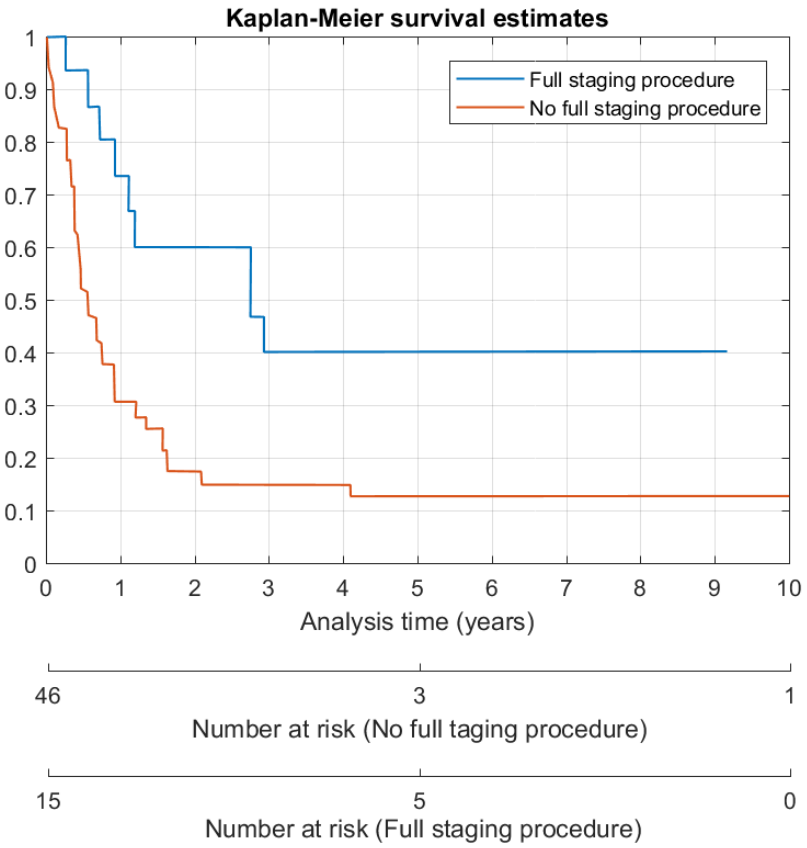

Figure 5-5: Overall survival according to receiving a full staging procedure

6 Discussion

In this study, a descriptive account of patients treated for uterine carcinosarcoma in our unit over a period of 10 years, was presented. Clinical characteristics, surgical-pathological factors, treatment, follow-up and survival data were presented. Important prognostic factors associated with PFS and OS were identified.

The 5-year overall survival of 19.7% is much worse than what is described in the international literature, with 5-year survival ranging from 33 to 39%[7,8]. Reasons for this is unclear, but differences in tumour biology or patient genetics in our population might be at play. Also, 62.3% of patients presented with advanced disease (FIGO III and IV). Poor access to services may be the cause of the late presentation. A 2-year progression-free survival appears to be more realistic given the high mortality of patients, as this was the same as the 5-year progression-free survival of 17.3%.

Important risk factors that have been associated with uterine carcinosarcoma (obesity, nulliparity, exogenous estrogen use, the protective effect of oral contraceptives, association with tamoxifen therapy and previous radiotherapy)[19–24] were present in our population. The mean BMI of the cohort was 32.86 and 2 patients had a history of tamoxifen use. However, nulliparity (median parity was 4) and a history of previous pelvic radiotherapy were not present. There was a high incidence and spectrum of comorbid diseases related to obesity in the study population (hypertension, diabetes, ischemic heart disease and hypercholesterolemia).

The poor performance of pap smear as a screening test in detecting uterine malignancy is well known and it is not used for this indication. The sensitivity of 65.91% of a pap smear in detecting uterine malignancy was surprisingly high. But all patients were symptomatic, and this was not used as screening.

Of the entire cohort, 82% of the patients received surgery and only 54% of the patients received some sort of other therapy, either as part of curative treatment or as part of symptom palliation. It is well established that surgery is the cornerstone of treatment of any uterine cancer and complete debulking should be the primary goal. The heterogeneity in which and how patients received other types of therapy demonstrate the lack of evidence supporting adjunctive treatment and highlights the need for universal, evidence-based protocols. Although several retrospective series and prospective non-randomized trials on treatment and outcome have been published[50,51,55–64,66,67], only 3 prospective randomized trials are available to guide treatment and a fourth is ongoing. The first is a Gynecologic Oncology Group randomized phase III trial of whole abdominal irradiation (WAI) versus cisplatin-ifosfamide and mesna (CIM) as post-surgical therapy in stage I-IV uterine carcinosarcoma[52]. The trial did not find a statistically significant advantage in recurrence rate or survival of adjuvant CIM over WAI. Another GOG randomized phase III trial in advanced uterine carcinosarcoma demonstrated a superior OS for combination chemotherapy (ifosfamide with paclitaxel) compared with single-

agent treatment (ifosfamide alone)[53]. A Phase 3 randomized study conducted by the European Organisation for Research and Treatment of Cancer evaluated the role of adjuvant pelvic radiotherapy for early-stage uterine sarcomas (including 91 patients with UCS)[68]. The study confirmed a trend towards better local control (but also higher distant metastatic rate) and no significant impact on either PFS or OS. GOG 261, the latest randomized phase III trial comparing the combination of carboplatin and paclitaxel versus the combination of ifosfamide and paclitaxel for UCS, is ongoing (NCT00954174).

The recurrence rate of 27.9% in our series is lower than that reported in other studies. Yamada et al.[37] reported a recurrence rate of 55% and the majority of these (42%) had an extra-pelvic component. More recent studies also reported higher recurrence rates (44.7%) with 55% of recurrences being extra-pelvic[38]. Our recurrence rate most likely represents an underestimate of the true recurrence rate as the overall survival was poor. As death is a competing risk for progression, this was considered and incorporated in the survival analysis. A large percentage of patients most likely died from aggressive disease before a recurrence could be identified. However, in the recurrence group, 70.6% of patients presented with recurrence not confined to the pelvis. Of this group, only 33.3% had initial chemotherapy as adjuvant treatment. It appears that we are not using enough chemotherapy in our setting. Of the 5 patients (29.4%) that presented with local recurrence, none had adjuvant treatment. As adjuvant treatment was individualized based on several factors and not standardized, it is difficult to make conclusions about optimal adjuvant treatment. However, the failure pattern of carcinosarcoma (in our study and others above), appear to favour a high rate of local and/or distal relapse. Many retrospective case series and prospective non-randomized published reports[69–79] suggested a longer survival with a combination of radiation and chemotherapy regimens. The schedule and sequence remain controversial across these studies and no quality of life studies are available on the toxicity profile combining these two radical treatment modalities.

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In the univariate analysis of PFS, only tumour diameter ≥ than 100mm was significant for progression. In the multivariate analysis of PFS, this association was questionable (see results section). Full staging surgery was also associated with risk of progression of disease.

In the univariate analysis of OS, several variables were statistically significant. A positive family history, receiving a full staging operation, and receiving any other modality of treatment was associated with better survival. An abnormal pap smear, late stage disease, presence of residual tumour, myometrial invasion of more than 50%, cervical involvement and adnexal involvement was associated with higher risk of death. In multivariate analysis, advanced stage was associated with poorer overall survival. Receiving a full staging laparotomy and receiving any other modality of treatment (with or without surgery) significantly reduced the risk of death.

Several studies[9,37–43,49,67] have reported on pathological and clinical factors predictive of recurrence and survival. Among these, age, stage, Ca125 level, myometrial invasion, LVSI, positive cytology, adnexal involvement, serosal involvement, lymph node involvement, number of lymph nodes harvested, tumour size, adjuvant radiotherapy, poor performance status, postsurgical residual tumour size greater than 1cm, histologic cell type (heterologous versus homologous), were all shown to carry prognostic significance.

The impact of advanced stage on recurrence-free and overall survival is well known, but we could not confirm the prognostic significance of older age with poorer disease-free and overall survival.

The data confirmed that a full staging laparotomy (including pelvic lymphadenectomy) has a significant effect on overall survival. Although the significance of the number of lymph nodes harvested could not be tested due to limited patient cohort, the mean lymph node yield per patient was high (19). Some studies have confirmed that lymphadenectomy offers a measurable survival benefit beyond staging information[7]. This may be related to the therapeutic benefit that has been alluded to in the benefit of lymphadenectomy in other high-risk endometrial cancers as well[83]. In a matched cohort analyses in stage 1 UCS (5 614 women identified from the National Cancer Database)[78], it was concluded that the removal of at least 15–20 lymph nodes are associated with increased survival. One of the largest multi-institutional retrospective studies to date from the Japanese Gynecologic Oncology Group[41], examined prognostic factors in 486 patients with stage I-IV uterine carcinosarcoma and concluded pelvic lymphadenectomy was associated with improved DFS and OS and may be necessary for the surgical management of UCS. Para-aortic lymphadenectomy did not influence these parameters. A large SEER-based analysis[67] (including 1 855 patients with Stage I-III uterine carcinosarcoma) showed that disease-free survival and five-year overall survival (49% vs 34%) were significantly improved for patients receiving lymph node dissection compared to patients that received no lymph node dissection. This is an important finding for several reasons. Controversy exists regarding the necessity and type of lymphadenectomy that should be performed in patients with uterine carcinosarcoma. In our own dataset, lymph node metastases were present in 26.67% of patients that did undergo a pelvic lymphadenectomy. Also, in an old GOG[9] study of 301 patients with uterine carcinosarcoma, 20 % of patients with early-stage disease already had lymph node metastasis. In our cohort, full staging was done equally across stages (53.33% in stage I-II UCS and 46.67% in patients with stage III-IV UCS), minimizing the risk of selection bias with this result.

The finding of full staging surgery relating to a significant risk of progression of disease seems contradictory. Because full staging surgery was associated with such a significant survival benefit, more patients were alive in this group to experience the event of progression. This also highlights the importance of accurate pre-operative histology to guide appropriate surgery.

Full staging laparotomy, including pelvic adenectomy, is therefore necessary for accurate staging and improved survival outcomes. Patients with uterine carcinosarcoma should be managed in tertiary centers with the necessary surgical expertise. The guidelines offered by the NCCN are also in support of this surgical approach in uterine carcinosarcoma[45].

The finding that patients who receive any other modality type of treatment (for curative or palliation intent, with or without surgery) have better overall survival, highlights the important principle that uterine carcinosarcoma is responsive (at least partially) to chemotherapy and radiation therapy. However, we need to be careful to draw conclusions from our small sample size. Perhaps better prognosis patients received treatment. Other modality therapy should be considered and offered to patients, even if the situation seems futile due to advanced or unresectable disease.

Our study had several limitations. It was a retrospective study, which may be prone to biases. Surgical and adjuvant treatments were not standardized. It consisted of a small sample size with incomplete data sets. This limited our statistical analysis in evaluating prognostic data and may have increased selection bias.

Strengths included that we had 5-year outcome data available on the entire cohort. All the histological data were reviewed by an expert in gynaecological malignancies. To our knowledge, this is the first series review of this type of tumour on the African continent.

In conclusion, uterine carcinosarcoma carries much worse survival in our population than what is quoted in the international literature. Standard protocols need to be developed in managing these cancers. They need to be managed in tertiary, high-volume centers with expertise in gynecological oncology surgery. Full staging surgery (including TAH, BSO, pelvic lymphadenectomy and omental evaluation) carries a significant survival benefit. Patterns of recurrence and the survival benefit of modalities other than surgery alone, suggest the need for adjuvant local control modalities and systemic treatment to decrease recurrence and improve survival. After interpreting the data, it is clear that the management of these patients need to be better in terms of surgical intervention and the incorporation of more aggressive adjunctive treatment modalities.

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